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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
O'DELL, DAVID K	
ART UNIT	PAPER NUMBER
1625	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/546,005	STARKE ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6,7,12,13 and 18* is/are pending in the application.

4a) Of the above claim(s) *13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6,7,12 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 4, 6-7, 12, 13, 18 are pending in the current application. Claim 13 is withdrawn from consideration.

Response to Restriction/Election

2. The restriction requirement was modified on 4/23/3008. The applicant has elected example 1, as the species of Example 1 (Example 1, was previously named as a different compound, but was corrected). The claims of 2/23/2008 were entered with the response and amendment and are those under examination. The revised restriction requirement affects none of the current rejections of record, since it only effectively adds material to the elected group (i.e. formula IB).

Group I, Claims 1, 3-9, 12 & 18 drawn to compounds and compositions possessing a benzothiazepine core where in applicant's Markush structure of Formula I M^1 is CH_2, M^2 is NR^{24}, R^1 and R^2 are H or lower alkyl, R^4=R^7=R^9=R^8=R^{14}=R^{15} =R^{24}=H, one of R^5 or R^6 is H or SMe and the other is IA, Z is O, R^{10} is cyclohexyl or phenyl, n=1, m=0, R^{13} is IB p=1, q=0, R^{16} is OH, r=3, R^{17} is C_{1-10}alkyl, said alkyl being ethyl and substituted with two R^{47}'s (one on each carbon), where both R^{47}'s are selected from hydroxy shown as structures **IA** and **IB** in Figure 1. If this group is elected, a single disclosed species is also required.

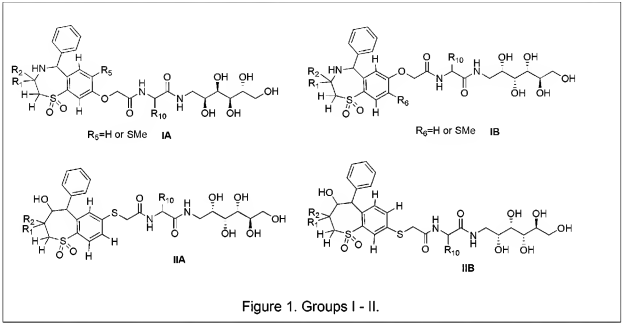
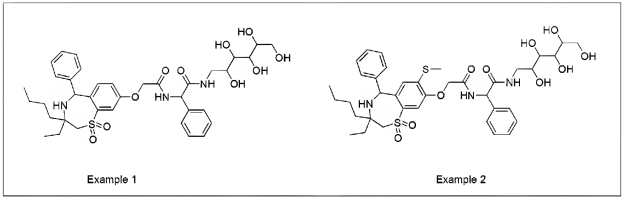


Figure 1. Groups I - II.

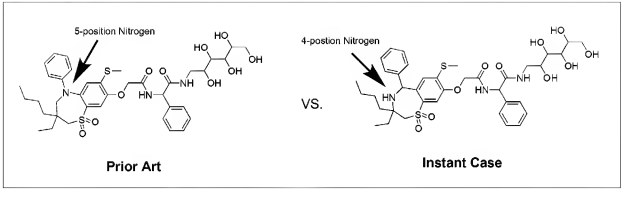


Claim Rejections/Objections Withdrawn

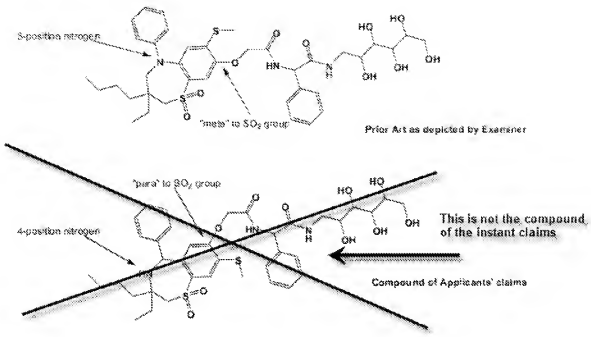
3. The rejections of claims 1, 4, 6-7, 12, & 18 under 112 2nd paragraph for prodrug is withdrawn.

Claim Rejections/Objections Maintained/ New Grounds of Rejection

4. The rejections of claims 1, 4, 6-7, & 18 under 112 1st paragraph for scope of enablement is maintained as the number of examples, namely two, does not support the vast scope claimed, for the reasons of record and contra to the applicants' assertion the amendments do not overcome the rejection. The rejection of claims 1, 4, 6-7, 12 & 18 under 35 U.S.C. 103(a) as being obvious over Starke et. al. WO 2003020710, is maintained. The applicants' representative has argued that two changes are needed in the prior art compound, which is incorrect. The difference is again shown graphically below:



The structures drawn in the applicants remarks of 2/28/2008 are in error. They are reproduced below:



The compound of claim 12 is the 7-thiomethyl derivative. The 7 thiomethyl is actually para to the sulfur and the IA group is meta as shown in the examiners drawing, not as shown in the drawing in the remarks of 2/28/2008 .

A new rejection under 112 2nd paragraph is made for the "in-vitro hydrolysable ester or amide".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 3-9, 12 & 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "in-vitro hydrolysable ester or amide" is indefinite. The issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "in-vitro hydrolysable ester or amide" are molecules whose structure lie

outside the subject matter of formula 1, but upon metabolism in the body are converted to active compounds falling within the structural scope of formula 1. The claim describes the function intended but provides no specific structural guidance to what constitutes these esters or amides. Esters or amides may come from forming bonds between amino groups and acids. It is unclear which acids, alcohols, or amines are involved. It is unclear if the esters, for example, are formed from alcohol groups on Formula I or where the alcohol groups are attached, and no structure of the required acids is disclosed. It may also be that acid groups are on the Formula I, forming esters with undisclosed alcohols. The ester or amide does not refer to a compound but rather is a name for a functional group. Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claims 1, 3-9, 12 & 18. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 4, 6-7, & 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents. The compounds that are enabled for synthesis are as follows:

M^1 is CH_2, M^2 is NR^{24}, R^1 and R^2 are H or lower alkyl, R^4=R^7=R^9=R^8=R^{14}=R^{15}=R^{24}=H, R^6 is H or SMe, R^5 is IA, Z is O, R^{10} is cyclohexyl or phenyl, n=1, m=0, R^{13} is IB p=1, q=0, R^{16} is OH, r=3, R^{17} is $C_{1\text{-}10}$alkyl, said alkyl being ethyl and substituted with two R^{47}'s (one on each carbon),

where both R^{47}'s are selected from hydroxy, v =0, and the R10 is optionally substituted by halogen, shown as structure **I.**

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are broad with respect to R3 which may be these multiple substituents in the case of R10 bearing R28's and R29's etc. **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should have activity at the IBAT. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic/medicinal chemist. **(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** Each one of the factors (**C**, **E-H**) will be discussed in light of the scientific literature when such a factor is being directly pointed to a large capital letter referring to the aforementioned Wands factor will be placed directly after such a remark or explication.

The medicinal chemistry of IBAT in regard to the class of benzothiazepines is well-developed and many limitations are well known in the art. In particular the phenyl ring (R3 substituents, where v is other than 0) is sensitive to structural effects Tollefson et. al. "A Novel Class of Apical Sodium Co-dependent Bile Acid Transporter Inhibitors: The 1,2-Benzothiazepines" *Bioorganic & Medicinal Chemistry Letters* **2003**, *13*, 3727–3730:

> "It was quite evident that the R sulfonamido substituent has a substantial effect on the potency of these compounds (seeTable 1). The benzyl substituted compounds (17a and 17b) exhibited weak inhibition in vitro (IC50>1000 nM). The smaller methyl group (16a–k) was a bit more active showing moderate to weak in vitro activities (IC50=320–1200 nM). The secondary sulfonamides 15a–h (R=H) were found to be the most potent compounds in this series as their activities were 20–50 times more potent than their respective N-methyl analogues (IC50=3–44 nM). We believe this to be a purely steric effect due to the low activity when R=benzyl or R=methyl. The sulfonamido nitrogen may be in close proximity to the surface of the binding site. Hydrogen bonding at the sulfonamido nitrogen appears not to contribute to binding as illustrated by 1,4- and 1,5-benzothiaepines (2 and 3).
> A modest electronic effect of the lower 5-aryl ring was observed. The electron withdrawing 30-NO2 group (15b, IC50=44 nM) had slightly less or comparable activity than the unsubstituted phenyl ring (15a, IC50=35). The electron donating 30-NH2 (15c IC50=6 nM) and 40-OH (15e, IC50=3 nM) showed a 5-10 fold increase in activity compared to the unsubstituted phenyl ring 15a. However, the decreased activity of the 40-OMe analogue (15d, IC50=26 nM) may indicate that the proper placement of the hydrogen as a H-bond donor is required. A similar trend was noted for tertiary sulfonamide (R=Me, see compounds 16a–e). However, the 40-OMe analogue (16d, IC50=570 nM) is equipotent with the 40-OH analogue (16e, IC50=580 nM) unlike in the secondary sulfonamides (R=H). The negative interaction of the N–Me substituent with the transporter changes

> the orientation of the inhibitor. This altered alignment prevents the beneficial binding of the 40-OH group as seen in the secondary sulfonamides.
> Efforts to prepare a more water soluble 1,2-benzothiazepine resulted in the synthesis of more potent ASBT inhibitors. Several side chains linking a quaternary ammonium salt to the 5-phenyl ring were investigated. An amide linker was constructed from the 3-amino compounds (15c and 16b) and then reacted with triethylamine to afford 15g, 16h and 16i. The quaternary ammonium salts (15g, 16h and 16i) exhibited potencies 3–14 times greater than their alkyl halide precursors (15f, 16f and 16g) indicating the importance of the ammonium group for optimal activity. It is also important to note that the potencies of 15g, 16 h and 16i are substantially better than the simple 30-NO2 and 30-NH2 precursors (15b, 15c, 16a, and 16b), and that 15g is one of the most potent compounds to date (IC50=1.6 nM). We believe that the quaternary ammonium salt may be exposed to solvent and its main function to be increased solubility.
> A polyethylene glycol linker was examined at the 40-position of the 5-phenyl ring with a quaternary ammonium salt attached to its end as well. Once again these compounds (15h, 16j and 16k) show greater potency than the corresponding 40-OH compounds (15d and 16d). It appears that one can substitute a fairly large substituent on the 5-phenyl ring as long as water solubility is maintained.
> The 1,2-benzothiazepines 1,1-dioxides are a novel class of ASBT inhibitors that show nanomolar activities in vitro. Further evaluation is needed in this series in order to determine the in vivo utility of this novel class of ASBT inhibitors." Pg. 3728-3729 **(C & E)**

We have not been given any information in regard to the molecular determinants of receptor affinity for the compounds of the instant case. In fact no assays have been performed. **(F & G)** What are the important structural features for the claimed utility? The purpose of adding this side chain of the instant case (bearing polyols) to the benzothiazepine moiety is to decrease

intestinal absorption and alter the pharmacokinetics. However it is very clear that groups are claimed that would adversely affect this property (lipophilicity/water solubility), for example R3 can be a hexyl chain (C6 alkyl) and v can be 5, creating a compound that would be a very greasy (lipophillic and hence not water soluble), and one certainly would not expect it to be a active at the IBAT. **(H) Only one compound has been prepared. (G)**

WORKING EXAMPLES AND A CLAIMED GENUS For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

2164.03 Relationship of Predictability of the Art and the Enablement Requirement

[R-2] The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839,166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a 'specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." (citations omitted)).< The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated:

> [I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent

> references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.]

The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730,734, 169 USPQ 298, 301 (CCPA 1971). **However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims.** *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *Inre Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir.1991). This is because it is not obvious from the disclosure of one species, what other species will work.

The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has only a single examples in this unpredictable art without undue experimentation. **(C, E, F, G, H).** "A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 4, 6-7, 12, & 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Starke et. al. WO 2003020710 (cited on IDS). The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

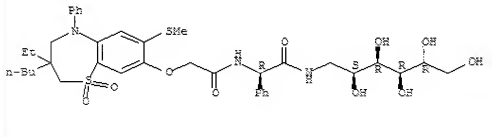
A) Determining the scope and contents of the prior art.
B) Ascertaining the differences between the prior art and the claims at issue.
C) Resolving the level of ordinary skill in the pertinent art.
D) Considering objective evidence present in the application indicating obviousness or nonobviousness.

A) Determining the scope and contents of the prior art:

The prior art teaches the compounds shown below:

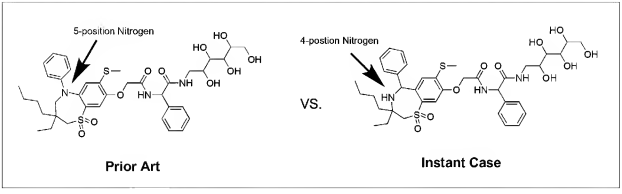
RN 501098-57-3 CAPLUS
CN D-Glucitol, 1-[[(2R)-[[[[3-butyl-3-ethyl-2,3,4,5-tetrahydro-7-(methylthio)-1,1-dioxido-5-phenyl-1,5-benzothiazepin-8-yl]oxy]acetyl]amino]phenylacetyl]amino]-1-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



B) Ascertaining the differences between the prior art and the claims at issue.

The difference between the prior art and the claims at hand (the only species of the instant case), is the position of the nitrogen atom in the ring. This can be seen graphically below:



C) Resolving the level of ordinary skill in the pertinent art: The level of ordinary skill is high. Someone preparing these compounds would be trained in organic chemistry and would recognize the very close structural similarity and would expect them to have similar properties.

D) Considering objective evidence present in the application indicating obviousness or nonobviousness:

Positional isomers, having the same radical on different positions of the molecule, are *prima facie* obvious, and require no secondary teaching. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these position isomers based on the expectation that such close analogues would have similar properties and upon the routine nature of such position isomer experimentation in the art of medicinal chemistry. It would be routine for the chemist to vary the point of attachment in order to increase potency and to establish better patent protection for her compounds. This situation is nearly exactly that found in *Ex parte Ullyot* 103 USPQ 185 (4-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline obvious over a reference teaching 4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline), "[p]osition isomers are recognized by chemists as similar materials",

quoted with approval by *Ex parte MOWRY AND SEYMOUR* 91 USPQ 219, *In re JONES* 74 USPQ 152 (4-methyl naphthyl-1-acetic acid and 2-methyl naphthyl-1-acetic acid obvious over a reference teaching 1-methyl naphthyl-2-acetic acid), *Ex parte BIEL* 124 USPQ 109 (N-ethyl-3-piperidyl diphenylacetate obvious over a reference teaching N-alkyl-4-piperidyl diphenylacetate), "[appellant's arguments] do not, in any way, obviate the plain fact that appellant's DACTIL is an isomer of McElvain et al.'s compound. This close relationship places a burden on appellant to show some unobvious or unexpected beneficial properties in his compound in order to establish patentability", *Ex parte Henkel* 130 USPQ 474, (1-phenyl-3-methyl-4-hydroxypyrazole obvious over reference teaching 3-phenyl-5-methyl-4-hydroxypyrazole), "appellants have made no comparative showing here establishing the distinguishing characteristics they allege which we might consider as evidence that the claimed compounds are unobvious. It is clear from *In re Henze*, supra, and the authorities it cites, that at least this much is necessary to establish patentability in adjacent homologs and **position isomers** (emphasis added)".

In re Surrey 138 USPQ 67, (2,6-dimethylphenyl-N-(3-dimethylaminopropyl) carbamate obvious over a reference teaching 2,4-dimethylphenyl N-(3-dimethylaminopropyl) carbamate), *In re MEHTA* 146 USPQ 284, (2-(1-methyl)-pyrrolidylmethyl benzilate obvious over a reference teaching 3-(1-methyl)-pyrrolidylmethyl benzilate), "[t]he fact that a **position isomer** (emphasis added) of a compound is known is some evidence of the obviousness of that compound. **Position isomerism** (emphasis added) is a fact of close *structural* (emphasis in original) similarity ...".*Deutsche Gold-Und Silber-Scheideanstalt Vormals Roessler v. Commissioner of Patents*, 148 USPQ 412, (1-azaphenothiazines obvious over references teaching 2-

azaphenothiazines, 3-azaphenothiazines, and 4-azaphenothiazines), *In re Crounse*, 150 USPQ 554 (dye with *para* ($CONH_2$) and *ortho* (OCH_3) obvious over a dye with the same nucleus and *meta* ($CONH_2$) and *para* (OCH_3) group), *Ex parte Allais*, 152 USPQ 66, (3-β-aminopropyl-6-methoxyindole obvious over a reference teaching 3-β-aminopropyl-5-methoxyindole), *In re Wiechert* 152 USPQ 247, (1-methyl dihydrotestosterones obvious over a reference teaching 2-methyl dihydrotestosterones), *Monsanto Company v. Rohm and Haas Company*, 164 USPQ 556, at 559, (3',4'-dichloropropionanilide obvious over references teaching 2',4'-dichloropropionanilide and 2',5'-dichloropropionanilide), *Ex parte Naito and Nakagawa*, 168 USPQ 437, (3-phenyl-5-alkyl-isothiazole-4-carboxylic acid obvious over a reference teaching 5-phenyl-3-alkyl-isothiazole-4-carboxylic acid), "[t]his merely involves **position isomers** (emphasis added) and under the decisions cited, the examiner's holding of *prima facie* obviousness is warranted." *In re Fouche*, 169 USPQ 429, (10-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene obvious over reference teaching 5-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene). *In re Hass* 60 USPQ 552, which found a *prima facia* case of obviousness of 1-chloro-1-nitrobutane over 1-chloro-1-nitroisobutane taught in the prior art, *In re FINLEY,* 81 USPQ 383, 2-ethyl hexyl salicylate over octyl salicylate.

Ex parte Engelhardt, 208 USPQ 343 at 349, "[i]f functional groups capable of withdrawing or repelling electrons are located in the chain or **ring** (emphasis added) of a biologically active compound, transfer of such groups to other positions in which their electronic effects are lessened or enhanced may alter the biological activity of the modified compound. Hence, **position isomerism** (emphasis added) has been used as a tool to obtain new and useful drugs", *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural

similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its analogs or isomers, either geometric isomers (*cis* v. *trans*) or **position isomers** (emphasis added) (*e.g. ortho v. para*)".

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1, 3-9, 12 & 18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 7,192,946. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds of the '946 application are position isomers of the instant case (see the 103 rejection *vide supra* for a detailed explanation).

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625